

REMARKS

The Final Office Action of August 10, 2004, has been received and reviewed. The applicants would like to thank the Examiner and his supervisor for the courtesy extended in the interview of September 7, 2004. Claims 2, 9, 10, 13-31, 35, 40 and 42-49 are pending in the application of which claims 23, 25 and 26 are withdrawn from consideration. Claims 2, 9, 10, 13-22, 24, 27-31, 35, 40 and 42-49 stand rejected. Applicants propose to amend claims 35, 40 and 42 as set forth herein. In the event that the Examiner enters the amendments to claims 35, 40 and 42, applicants will consider canceling claims 44-49. All amendments are made without prejudice or disclaimer. Reconsideration is requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 2, 9, 10, 13-22, 24, 27-31, 35, 40 and 42-49 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly lacking enablement for an antibody or fragment thereof which binds to an epitope under broadly recited conditions. Applicants respectfully traverse the rejections.

The Final Office Action asserted that the specification is “enabling for an antibody or fragment thereof and composition comprising said antibody or fragments which binds to an epitope and broken from an epitope under specifically chosen conditions recited in Table 1.” (Final Office Action, page 2). Although applicants do not agree that any of the claims lack enablement, to expedite prosecution, applicants propose to amend independent claims 40 and 42 as set forth herein.

As proposed to be amended, independent claim 40 is directed to a selected monoclonal antibody, or fragment thereof, that has been selected for its ability to bind to an epitope at a first pH of 8.5 and such that the bond of the selected monoclonal antibody, or fragment thereof, to the epitope is broken at a second pH of 7. Table 4 of the as-filed specification indicates that clone 3 is able to bind to and disassociate from an epitope under the selection conditions of B, C and D of Table 1. (*See, Specification* as-filed, Table 4, page 11). Table 1 of the as-filed specification indicates that C has binding conditions of a pH of 8.5 and 1M NaCl, and elution conditions of a pH of 7 (e.g., Milli Q), and D has binding conditions of a pH of 8.5 and elution conditions of a pH of 4.5 and 1M NaCl. (*See, Id.* at Table 1, page 7). Since clone 3 was selected under both

conditions C and D, a binding pH of 8.5 and an elution condition of a pH of 7 are specifically disclosed.

Since the as-filed specification discloses a working example of the antibody, or fragment thereof, of amended claim 40, one of ordinary skill in the art would be able to make and use the selected monoclonal antibody, or fragment thereof, of claim 40 without undue experimentation. Reconsideration and withdrawal of the enablement rejection of claim 40 are requested.

Turning to amended, independent claim 42, it has been amended to be directed to a selected monoclonal antibody, or fragment thereof, that has been selected for its ability to bind an epitope at a first pH of 8.5 and such that the bond of the selected monoclonal antibody, or fragment thereof, to the epitope is broken at a second pH of 4.5 and an ion strength of 1M NaCl. Since the as-filed specification discloses multiple working examples (*e.g.*, clones 47, 51, 5, 14 and 3 were shown to satisfy the conditions of selection D) of an antibody, or fragment thereof, as recited in amended claim 42 at Tables 1 and 4, one of ordinary skill in the art would be able to make and use the selected monoclonal antibody, or fragment thereof, of amended claim 42 without undue experimentation. (*See, Id.* at pages 7 and 11).

Reconsideration and withdrawal of the enablement rejection of amended claim 42 are requested.

Dependent claims 2, 9, 10, 13-22, 24, 27-31, 35, and 43-49 should be enabled, at the very least, as depending from enabled independent claim 40 or 42. Thus, reconsideration and withdrawal of the enablement rejections of claims 2, 9, 10, 13-22, 24, 27-31, 35, and 43-49 are requested.

Rejections under 35 U.S.C. § 103

Claims 2, 9, 10, 13-22, 28, 30-31, 35, 40 and 42-49

Claims 2, 9, 10, 13-22, 28, 30-31, 35, 40 and 42-49 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Beggs et al. in view of Goding. Applicants respectfully traverse the rejections.

The Final Office Action asserted that Beggs et al. teaches an antibody that is able to bind to a target site through antibody-antigen binding at conditions lie within physiologically acceptable limits ... pH of between 6 and 8 would be

considered by one of ordinary skill in the art to lie within physiological limits ... Goding teaches that during optimization of each purification protocol for each antibody of interest and a fragment thereof, the parameters such as pH and ionic strength play an essential role and that it is an inherent properties of all antibody and fragment to bind to an epitope under one set of specifically chosen conditions and be eluted from an epitope ... under specifically chosen different conditions.

(Final Office Action at pages 5-6).

Although applicants do not agree that a *prima facie* case of obviousness has been established for any of the pending claims, to expedite prosecution, applicants propose to amend independent claims 40 and 42 as set forth herein. As amended, claim 40 is directed to a selected monoclonal antibody, or fragment thereof, that has been selected for its ability to bind to an epitope at a first pH of 8.5 and such that the bond of the selected monoclonal antibody, or fragment thereof, to the epitope is broken at a second pH of 7.

A *prima facie* case of obviousness cannot be established since the cited references do not alone, or in combination, teach or suggest each and every element of amended claim 40. For instance, amended claim 40 recites that the selected monoclonal antibody, or fragment thereof, binds to an epitope at a first pH of 8.5. As stated in the Final Office Action “Beggs et al, teach an antibody and antibody fragment ... that are able to bind to a target site through antibody-antigen binding at conditions lie within physiologically acceptable limits ... pH of between 6 and 8 would be considered by one of ordinary skill in the art to lie within physiological limits.” (Final Office Action at page 5). Since amended claim 40 recites a binding pH of 8.5 and Beggs et al. does not, alone or in combination with Goding, teach or suggest binding at a pH of 8.5, the cited references do not teach each and every element of amended claim 40 as required to establish a *prima facie* case of obviousness.

Further, the cited references do not alone, or in combination, teach or suggest an antibody, or fragment thereof, having a bond between the antibody, or fragment thereof, and epitope broken at a pH of 7 as recited in amended claim 40. In formulating the obviousness rejection, the Office Action indicated that “it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine all operable and optimal range[]s of pH and ion strength at which antibody of fragment thereof binds to and eluted from an epitope, and

taught by Goding and use it for the antibody or fragment thereof of Beggs et al.” (Final Office Action at page 6).

Further, during the interview of September 7, 2004, the Examiner reasoned that in view of the Goding reference, which indicates that all antibodies inherently disassociate from their epitope at some condition, it is **possible** that the antibodies of Beggs et al. would disassociate at a pH of 7. However, that is not the standard of the theory of inherency. As stated by the Federal Circuit

to establish inherency, the extrinsic evidence ‘must make clear that the missing descriptive matter is **necessarily present** in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, **may not be established by probabilities or possibilities**. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

(MPEP § 2112, *quoting In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (emphasis added)). Since the Goding reference does not refer to the antibodies of Beggs et al., the cited references do not establish that the antibodies of Beggs et al. **necessarily** disassociate a pH of 7. Thus, the theory of inherency cannot be used to establish that the cited references teach or suggest each and every element of amended claim 40.

Further, to establish a *prima facie* case of obviousness, there must be a **reasonable expectation** of success. (See, MPEP § 2141, page 2100-120). The rationale that the antibody of Beggs et al. will bind at a pH of 6-8 and disassociate at a pH of 7 is not supported by the references. For instance, the Goding reference, on which the Office is relying indicates that in the majority of the cases it may be expected that harsh conditions for elution of antigen will be requested. (See, Goding, page 231). Thus, one of ordinary skill in the art would not reasonably expect the antibodies of Beggs et al., which bind at physiological conditions (which the Final Office Action indicates are a pH of 6-8), to dissociate at a pH of about 7 (i.e., a physiological condition) as recited in claim 40 since Goding indicates that in the majority of cases, it is expected that much harsher conditions are required to elute an antibody from its antigen. An elution pH of 7 is not much harsher than a pH of 6-8. Thus, no reasonable expectation of success exists in assuming that the antibodies of Beggs et al. would dissociate at a pH of 7 as recited in claim 40.

Turning to amended, independent claim 42, it also cannot be rendered obvious since Beggs et al. and Goding do not alone, or in combination, teach or suggest each and every element of amended claim 42. As amended, claim 42 is directed to a selected monoclonal antibody, or fragment thereof, that has been selected for its ability to bind an epitope at a first pH of 8.5 and such that the bond of the selected monoclonal antibody, or fragment thereof, to the epitope is broken at a second pH of 4.5 and an ion strength of 1M NaCl.

As previously established herein, Beggs et al. is limited to binding of an antibody at a pH which the Office indicates is a pH of 6-8. (*See, Final Office Action* at page 5). Since claim 42 recites a binding pH of 8.5, Beggs et al. does not alone, or in combination with Goding, teach or suggest a binding pH of 8.5.

Further, the cited references do not teach or suggest disassociation conditions at a second pH of 4.5 and an ion strength of 1M NaCl as recited in amended claim 42. The Final Office Action asserted “it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine all operable and optimal range[]s of pH and ion strength at which antibody or fragment thereof binds to and eluted from an epitope, and taught by Goding and use it for the antibody or fragment thereof of Beggs et al.” (*Final Office Action*, page 6). However, as stated in the MPEP a “statement that modifications of the prior art to meet the claimed invention would have been “well within the ordinary skill of the art at the time the claimed invention was made”” because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness.” (MPEP § 2143.01, page 2100-131) (emphasis in original). Thus, a *prima facie* case of obviousness cannot be established for independent claim 42.

Since dependent claims 2, 9, 10, 13-22, 28, 30-31, 35, and 43-49 include the elements of independent claim 40 or 42, and a *prima facie* case of obviousness cannot be established with regard to claim 40 and 42, a *prima facie* case of obviousness also cannot be established with regard to any of dependent claims 2, 9, 10, 13-22, 28, 30-31, 35, and 43-49.

Reconsideration and withdrawal of the obviousness rejections of claims 2, 9, 10, 13-22, 28, 30-31, 35, 40 and 42-49 are, thus, requested.

Claims 2, 9, 10, 13-21, 24, 27, 28, 30, 31, 35, 40 and 42-49

Claims 2, 9, 10, 13-21, 24, 27, 28, 30, 31, 35, 40 and 42-49 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Cummins et al. in view of Goding. Applicants respectfully traverse the rejections.

A *prima facie* case of obviousness cannot be established for any of the claims since Cummins et al. does not alone, or in combination with Goding, teach or suggest each and every element of amended, independent claim 40 or 42. As amended, claim 40 is directed to a selected monoclonal antibody, or fragment thereof, that has been selected for its ability to bind to an epitope at a first pH of 8.5 and such that the bond of the selected monoclonal antibody, or fragment thereof, to the epitope is broken at a second pH of 7.

Cummins et al. does not alone, or in combination with Goding, teach or suggest each and every element of amended claim 40. The Final Office Action indicates that “Cummins et al. teach various binding conditions that lie within physiologically acceptable limits, including pH and ion strength ... pH of between 6 and 8 would be considered by one of ordinary skill in the art to lie within physiological limits.” (Final Office Action at page 7). As amended, independent claim 40 has a binding condition of a first pH of 8.5 which does not fall within the binding conditions of Cummins et al. as stated in the Final Office Action. Further, Cummins et al. does not alone, or in combination with Goding, teach or suggest disassociation of the monoclonal antibody, or fragment thereof, from an epitope at a pH of 7 as recited in amended claim 40. Thus, the cited references do not teach each and every element of amended claim 40 as required to establish a *prima facie* case of obviousness.

A *prima facie* case of obviousness also cannot be established since no reasonable expectation exists in combining the cited references. The Final Office Action alleged that “it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine all operable and optimal range[]s of pH and ion strength at which antibody or fragment thereof binds to and eluted from an epitope, as taught by Goding and use it for antibody or fragment thereof taught by Cummins et al.” (*Id.*).

However, one of ordinary skill in the art would not have a reasonable expectation of success in assuming that the antibodies of Cummins et al. would dissociate at a pH of 7 as recited in claim 40 in view of Goding. For instance, the Goding reference, on which the Office is relying

indicates that in the majority of cases it may be expected that harsh conditions for elution of antigen will be required. (See, Goding, page 231). Thus, the antibodies of Cummins et al. that bind at physiological conditions (which the Final Office Action indicates are a pH of 6-8) would not be expected to dissociate at a pH of about 7 as recited in claim 40 since Goding indicates that in the **majority** of cases, it is **expected** that much harsher conditions are required to elute an antibody from its antigen. Since a pH of 7 is not much harsher than a pH of 6-8, a reasonable expectation of success does not exist to establish a *prima facie* case of obviousness.

Independent claim 42 also cannot be rendered obvious since Cummins et al. and Goding do not alone, or in combination, teach or suggest each and every element of amended claim 42. As amended, claim 42 is directed to a selected monoclonal antibody, or fragment thereof, that has been selected for its ability to bind an epitope at a first pH of 8.5 and such that the bond of the selected monoclonal antibody, or fragment thereof, to the epitope is broken at a second pH of 4.5 and an ion strength of 1M NaCl.

As established herein, Cummins et al. is limited to binding of an antibody at physiological pH which the Office indicates is a pH of 6-8. (See, Final Office Action at page 5). Since claim 42 recites a binding pH of 8.5, Cummins et al. does not alone, or in combination with Goding, teach or suggest a binding pH of 8.5.

Further, the Cummins et al. and Goding references do not teach or suggest disassociation conditions at a second pH of 4.5 and an ion strength of 1M NaCl as recited in amended claim 42. The Final Office Action asserted “it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine all operable and optimal range[]s of pH and ion strength at which antibody or fragment thereof binds to and eluted from an epitope, and taught by Goding and use it for the antibody or fragment thereof taught by, Cummins et al.” (Final Office Action, page 6).

However, as stated in the MPEP a “statement that modifications of the prior art to meet the claimed invention would have been “well within the ordinary skill of the art at the time the claimed invention was made”” because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness.” (MPEP § 2143.01, page 2100-131) (emphasis in original). Since the cited

references do not teach or suggest each and every element of amended claim 42, a *prima facie* case of obviousness cannot be established.

Since dependent claims 2, 9, 10, 13-22, 28, 30-31, 35, and 43-49 include the elements of independent claim 40 or 42 and a *prima facie* case of obviousness cannot be established with regard to claim 40 and 42, a *prima facie* case of obviousness also cannot be established with regard to any of dependent claims 2, 9, 10, 13-22, 28, 30-31, 35, and 43-49.

Reconsideration and withdrawal of the obviousness rejection of dependent claims 2, 9, 10, 13-22, 28, 30-31, 35, 40 and 42-49 are requested.

Claim 29

Claim 29 stands rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Beggs et al. in view of Goding, and further in view of Cole et al. Applicants respectfully traverse this rejection.

Since a *prima facie* case of obviousness cannot be established with regard to independent claim 40 from which claim 29 depends and claim 29 includes the elements of claim 40, a *prima facie* case of obviousness also cannot be established with regard to dependent claim 29.

Reconsideration and withdrawal of the obviousness rejection of claim 29 is requested.

Claim 43

Claim 43 stands rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Beggs et al. in view of Goding, and further in view of Fischer. Applicants respectfully traverse the rejection as set forth herein.

Since a *prima facie* case of obviousness cannot be established with regard to independent claim 40 from which claim 43 depends and claim 43 includes the elements of claim 40, a *prima facie* case of obviousness also cannot be established with regard to dependent claim 43.

Reconsideration and withdrawal of the obviousness rejection of claim 43 is requested.

ENTRY OF AMENDMENTS

The proposed amendments to claims 35, 40 and 42 should be entered because they are supported by the as-filed specification and do not introduce any new matter. The proposed amendments also should not require a further search because the proposed amendments regarding the pH were present in the pending pH range of the claims, and the added element directed to 1M NaCl was present in dependent claim 49. Further, as discussed at the interview of September 7, 2004, the proposed amendments should remove the enablement and obviousness rejections, thus, placing the application in condition for allowance.

As further discussed at the interview of September 7, 2004, if the Examiner determines that the proposed amendments do not remove the obviousness rejections, entry of the proposed amendments is requested since they certainly remove issues for appeal (*i.e.*, by removal of the enablement rejections, the only issue left for appeal would be the obviousness rejections).

CONCLUSION

In view of the proposed amendments and remarks, applicants submit that the claims define patentable subject matter and a notice of allowance is solicited. Should the Office determine that additional issues remain, the Office is kindly requested to contact the applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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